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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/498,098	STACK ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-38,40,50,55,60 and 80-87* is/are pending in the application.

4a) Of the above claim(s) *55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-38,40,50,55,60 and 80-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 10/20/03. Claim 10 has been cancelled. Claims 1, 60, 80 and 83 have been amended. New claim 87 has been added. Claims 1-9, 11-38, 40, 50, 55, 60 and 80-87 are currently pending in the application and are addressed herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

3. Claim 55 has previously been withdrawn from consideration for the reasons of record. Claims 1-9, 11-38, 40, 50, 60 and 80-87 are examined herein.

Claim Rejections - 35 USC § 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-9, 11-38, 40, 50, 60, and 80-87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 1 recites the limitations "the target protein" in line 16. There is insufficient antecedent basis for this limitation in the claim.

Claims 2-9, 11-22, 80, 83 and 85-87 depend on claim 1 and are therefore rejected for the same reasons. Appropriate correction is required.

6. Claim 23 recites the phrase "a α-NH-ubiquitin protein endoproteases" in lines 5-6 and 18-19. This phrase renders the claim indefinite because it is unclear if the claims are intended to encompass one or more α-NH-ubiquitin protein endoproteases.

Additionally, Claim 23 recites the limitation "said protein of interest" in line 21. There is insufficient antecedent basis for this limitation in the claim.

Claims 24-37 and 81 depend on claim 23 and are therefore, rejected for the same reasons. Appropriate correction is required.

7. Claim 38 recites the phrase "a α-NH-ubiquitin protein endoproteases" in line lines 5-6. This phrase renders the claim indefinite because it is unclear if the claim is intended to encompass one or more α-NH-ubiquitin protein endoproteases.

Claims 40, 82 and 84 depend on claim 38, and are therefore rejected for the same reason. Appropriate correction is required.

8. Claim 50 recites the limitation "said reporter moiety" in line 9. There is insufficient antecedent basis for this limitation in the claim.

Additionally, claim 50 recites the phrase "a α-NH-ubiquitin protein endoproteases" in line lines the last two lines. This phrase renders the claim indefinite because it is unclear if the claim is intended to encompass one or more α-NH-ubiquitin protein endoproteases.

Appropriate correction is required.

9. Claim 60 recites the limitation "said multimerized destabilization domain" in lines 2-3 and lines 7-8. There is only sufficient antecedent basis for "said linear multimerized destabilization domain" in the claim. Therefore, there is insufficient antecedent basis for the broader limitation "said multimerized destabilization domain" in the claim.

Additionally, claim 60 recites the phrase "a α-NH-ubiquitin protein endoproteases" in lines 3-4 and 9-10. This phrase renders the claim indefinite because it is unclear if the claim is intended to encompass one or more α-NH-ubiquitin protein endoproteases.

Additionally, claim 60 recites the limitation "said reporter moiety" in line 8. There is insufficient antecedent basis for this limitation in the claim.

Additionally, claim 60 recites the limitation "said linker" in lines 9 and 10. There is only sufficient antecedent basis for "said linker moiety" in the claim. Therefore, there is insufficient antecedent basis for the broader limitation "said linker" in the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-9, 11-38, 40 and 80-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-9, 11-22, 80, 83 and 85-87 are drawn to a method of detecting a protease activity in a cell, wherein the method uses a molecule comprising a destabilization domain wherein the destabilization domain can be **a ubiquitin homolog** (see claims 6-8). Additionally, the instant method encompasses a molecule comprising a reporter moiety wherein the reporter moiety can be **a naturally fluorescent protein homolog, a beta-lactamase homolog, a alpha-galactosidase homolog, an alkaline phosphatase homolog, a CAT homolog, and a luciferase homolog** (see claims 11-14)

Claims 23-37 and 81 are drawn to a method of regulating the concentration one or more target proteins in a cell, wherein the method uses a molecule comprising a destabilization domain wherein the destabilization domain can be **a ubiquitin homolog** (see claims 31-33).

Claims 38, 40, 82 and 84 are drawn to a method of destabilizing a target protein in a cell comprising administering to said cell a nucleic acid encoding a molecule comprising destabilization domain, wherein the destabilization domain can be **a ubiquitin homolog** (see claim 38 and 40).

It is noted that the specification defines homolog in the following manner,

> "The term 'homolog' refers to two sequences or parts thereof, that are greater than, or equal to 85% identical when optimally aligned using the ALIGN program. Homology or sequence identity refers to the following. Two amino acid sequences are homologous if there is a partial or complete identity between their sequences. For example, 85% homology means that 85% of the amino acids are identical when the two sequences are aligned for maximum matching. Gaps (in either of the two sequences being matched) are allowed in maximizing matching; gap lengths of 5 or less are preferred with 2 or less being more preferred. Alternatively and preferably, two protein sequences (or polypeptide sequences derived from them of at least 30 amino acids in length) are homologous, as this term is used herein, if they have an alignment score of more than 5 (in standard deviation units) using the program ALIGN with the mutation data matrix and a gap penalty of 6 or greater." (See pages 13-14 of the specification).

Therefore, the claims encompass molecules, including ubiquitin homologs, and reporter gene homologs, for which there is insufficient written description provided in the specification.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164).

In the instant case the claims encompass molecules including ubiquitin homologs and reporter gene homologs which can be as much as 15% different at the sequence level. Therefore, the claims encompass molecules which can vary in sequence by as much as 15%; however, the specification does not indicate which 15% of sequence can be varied without changing the desired function of the molecule. In order to meet the written description requirement in the instant case, the specification would have to indicate the relationship between the structure of the molecule and function of the molecule such that one of skill in the art could determine, without

performing additional experimentation, which homologs have the desired function and which homologs do not have the desired function. Here, the specification does not teach any structure-function relationship for the claimed homologs. Specifically, the specification does not teach the relevant structural/physical/chemical characteristics, such as the presence of certain functional domains or sequence motifs, which are critical to the function of the homologs. Therefore, the specification has not provided adequate written description for the homologs encompassed by the claims.

Specifically regarding the ubiquitin homologs encompassed by the claims, the specification has described a homolog of ubiquitin that has the desired function (retaining ubiquitin function while being non-cleavable by alpha-NH-ubiquitin-endoproteases). The specific ubiquitin homolog described by the specification is Ubiquitin G76V (a Gly to Val substitution at amino acid 76 of ubiquitin). Therefore, with respect to the rejection of claims drawn to ubiquitin homologs, amending the claim to limit the ubiquitin homolog Ubiquitin G76V would obviate this rejection.

Regarding the reporter gene homologs, the specification does not teach any homologs or the reporter genes contemplated. Amending the claims such that the claims were not drawn to the homologs would obviate this rejection. For instance, changing a naturally fluorescent protein homolog, a beta-lactamase homolog, a alpha-galactosidase homolog, an alkaline phosphates homolog, a CAT homolog, and a luciferase homolog to naturally fluorescent protein, beta-lactamase, alpha-galactosidase, alkaline phosphatase, CAT, luciferase, etc., would obviate the instant rejection.

12. Additionally, Claims 1-9, 11-38, 40 and 80-87 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As mentioned above, the claims molecules (i.e., homologs) for which there is insufficient written description provided in the specification. Without a clear description of the homologs encompassed by the claims, one of skill in the art would not know how to make or use the claimed invention without performing additional experimentation. The amount of additional experimentation is considered to be undue, when taking into consideration: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (See *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

In addition to, and separate from the rejection under 35 USC 112, first paragraph (written description), the following rejections under 35 USC 112, first paragraph (enablement) are also appropriate.

13. Claims 1-9, 11-22, 80, 83 and 85-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of detecting a protease activity in a cell, comprising:

1) providing a cell comprising:

a) at least one destabilization domain, wherein said at least one destabilization domain is non-cleavable by α-NH-ubiquitin protein endoproteases,

b) a reporter moiety, and

c) a linker moiety that operatively couples said at least one destabilization domain to said reporter moiety, wherein said linker moiety is non-cleavable by said α-NH-ubiquitin protein endoproteases, and wherein said linker moiety comprises a protease cleavage site, and

wherein said at least one destabilization domain, said reporter moiety and said linker moiety are encoded by one or more nucleic acid molecules in said cell, and

wherein cleavage of said protease cleavage site by a protease uncouples said at least one destabilization domain from said reporter moiety, thereby increasing the stability of said reporter moiety, and

2) detecting said reporter moiety, or a product of said reporter moiety, in said cell, wherein an increase of said reporter moiety, or a product of said reporter moiety, compared to a control cell is indicative of a protease activity in said cell;

does not reasonably provide enablement for the full scope currently encompassed by claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors considered in determining whether the disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

In the instant case, the claims are drawn to a method of detecting a protease activity in a cell comprising:

1) providing a cell comprising:

a) at least one destabilization domain, wherein said destabilization domain is non-cleavable by α-NH-ubiquitin protein endoproteases,

b) a reporter moiety, and

c) a linker moiety that operatively couples said destabilization domain to said reporter moiety,

wherein said linker moiety comprises a recognition motif for said protease activity and **modification** of said linker moiety by said protease activity **modulates** the coupling of said destabilization domain to said reporter moiety thereby **modulating** the stability of said reporter moiety, and

wherein said linker is non-cleavable by said α-NH-ubiquitin protein endoproteases, and wherein the destabilization domain, the target protein and the linker are encoded by one or more nucleic acid molecules in the cell,

2) detecting said reporter moiety, or a product of said reporter moiety, thereby detecting a protease activity in the cell. (Emphasis added for clarity).

It is noted that the instant claim encompasses **modification** of the linker moiety by the protease activity wherein modification could be an activity other than protease activity. However, the only known activity of the protease which would affect the coupling of the at least one destabilization domain to the reporter moiety is protease activity. Amending the claim to indicate that cleavage of the linker moiety (specifically cleavage of a protease cleavage site within said linker moiety) is recommended.

Additionally, the instant claims indicate that modification of the linker moiety by protease activity would **modulate** the coupling of the destabilization domain to said reporter moiety, thereby **modulating** the stability of said reporter moiety. It is noted that the term "modulate", as used here, encompasses both the ability to increase and the ability to decrease the coupling of the destabilization domain and the reporter moiety. However, the only affect that the protease activity could have on the coupling of the destabilization and reporter would be to decrease the coupling (which also could be viewed as increasing the uncoupling of the destabilization domain and the reporter moiety). One of skill in the art would not expect that a protease activity could increase the coupling of the destabilization domain and the reporter moiety of the instant system. It is noted that amending the claim, as indicated above, is recommended.

It is noted that making the recommended amendments such that the claims reads as indicated above would obviate the instant rejection.

14. Claims 23-37 and 81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for increasing the concentration of one or more target proteins in a cell, comprising:

1) providing a cell comprising,

a) a linear multimerized destabilization domain wherein said linear multimerized destabilization domain is non-cleavable by α-NH-ubiquitin protein endoproteases, and wherein said linear multimerized destabilization domain comprises at least two copies of a destabilization domain,

b) a target protein, and

c) a linker that operatively couples said linear multimerized destabilization domain to said target protein, wherein said linker is non-cleavable by α-NH-ubiquitin protein endoproteases, and wherein said linker comprises a protease cleavage site for a protease, and

wherein said at least one destabilization domain, said reporter moiety and said linker moiety are encoded by one or more nucleic acid molecules in said cell, thereby decreasing the stability of said target protein in said cell, and

wherein cleavage of said protease cleavage site by said protease uncouples said linear multimerized destabilization domain from said target protein,

2) providing said protease to cause cleavage of said protease cleavage site, thereby increasing the stability and concentration of said target protein in said cell,

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors considered in determining whether the disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

In the instant case, the claims are drawn to a method of **regulating** the concentration of one or more target proteins in a cell, comprising:

1) providing a cell comprising,

a) a linear multimerized destabilization domain wherein said linear multimerized destabilization domain is non-cleavable by a α-NH-ubiquitin protein endoproteases, and comprises at least two copies of a destabilization domain,

b) a target protein, and

c) a linker that operatively couples said linear multimerized destabilization domain to said target protein,

wherein said linker comprises a protease cleavage site for a protease and cleavage of said linker by said protease **modulates** the coupling of said linear multimerized destabilization domain to said target protein, and wherein the destabilization domain, the target protein and the linker are encoded by one or more nucleic acid molecules in the cell, thereby **modulating** the stability of said target protein in said cell, and

wherein said linker is non-cleavable by a α-NH-ubiquitin protein endoproteases,

2) providing said protease to cause cleavage of said linker, thereby increasing the stability and concentration of said protein of interest in said cell. (Emphasis added for clarity).

It is respectfully pointed out that the terms "regulating", "modulating" and "modulates" as used here, encompasses both the ability to **increase** and the ability to **decrease:** 1) the concentration of a target protein, 2) the coupling of the destabilization domain, and 3) the stability of the target protein. However, the specification only teaches, and one of skill in the art would recognize that cleavage of the linker (specifically the protease cleavage site within the linker) would only result in the uncoupling of the destabilization domain from the target protein, thus resulting in only the increase of the concentration of the target protein in the cell. Additionally, the specification only teaches, and one of skill in the art would recognize that when

the destabilization domain, linker and target protein are all coupled together, the only possible result would be a decrease in the stability of the target protein in the said. Finally, it is pointed out that the claim explicitly requires that a protease be provided to cause cleavage of said linker (see step 2). The method thus requires that a protease is provided to cause cleavage of the linker, and the only possible result of this step would be the increase in the stability and concentration of the target protein in the cell. Therefore, the steps set forth in the claims would not result in the **regulation** of the concentration of the target protein in the cell, but would only result in **increasing** the concentration of the target protein in the cell. . It is noted that amending the claim, as indicated above, is recommended.

It is noted that making the recommended amendments such that the claims reads as indicated above would obviate the instant rejection.

Response to Arguments

15. Applicant's arguments, see pages 13-19 of the response filed 10/20/03, with respect to the rejection of claims under 35 USC 112, (for lacking adequate written description of the activities encompassed by the claims) have been fully considered and are persuasive. The rejection previously set forth has been withdrawn.

16. Applicant's arguments, see pages 13-19 of the response filed 10/20/03, with respect to the rejection of claims under 35 USC 112, (for lacking enablement) have been fully considered and are persuasive for overcoming the rejection claims wherein the rejection was based on non-protease activity and detecting a reporter moiety in vivo. However, applicants' arguments with

respect to the rejection of claims for being drawn to **regulating** the concentration of a protein in a cell are not persuasive.

Applicants argue,

> "Applicants respectfully assert that one of the advantages of the present invention is that it allows for the careful regulation of protein concentration by controlling the number of ubiquitin moieties included (Page 5, lines 5-15). As indicated in the specification, by varying the number of destabilization domains present in the multimerized destabilization domain, it is possible to titrate the degree of destabilization, and therefore the steady state concentration of the target protein within a cell or transgenic organism (See e.g., Page 45, lines 21-30). Therefore, depending on whether the desired protein concentration in an organism is relatively high or relatively low, the number of copies of the destabilization domain can be determined (Page 60, lines 3-7): Furthermore, the specification provides experimental evidence of the ability to control protein concentration based on the number of destabilization domains included (Example 9, which starts on page 78). Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-38, 40, 50, 60, and 80-86 under 35 U.S.C. 112, first paragraph as allegedly not enabled by the specification." (See page 18 of the response).

In response, it is respectfully pointed out that the claims (indicated herein) are drawn to a method of regulating the concentration of a target protein in a cell wherein the method encompass providing a cell comprising (in general) a destabilization domain, a target protein and a linker that operatively couples the destabilization domain to the target protein. When the destabilization domain is coupled to the target protein (through the linker) then the target protein is destabilized and the concentration of the protein is low. The linker comprises a protease cleavage site such that when a protease cleaves the protease cleavage site, the destabilization domain dissociates (i.e., is uncoupled) from the target protein and results in an increase in stability or the target protein, and thus an increase in the concentration of the target protein.

Applicants assert that varying the number of destabilization domains makes it possible to "titrate the degree of stabilization" of the target protein. It is acknowledged that varying the number of destabilization domains would effect the stabilization of the target protein. However,

in order to be able to "regulate" the concentration of the target protein in a cell, one would have to be able to add destabilization domains to the target protein in the cell AND be able to remove the destabilization domains from the target protein as well. The claimed method for regulating the concentration of a target protein (see claims 23-37) does not include steps to add destabilization domains to the target protein *in the cell.* The method also explicitly indicates that a protease is provided to cause cleavage of the linker, which would only result in increasing stability and concentration of the target protein. Again, it is acknowledged the specification teaches that adding destabilization domains to the target protein can decrease stability/concentration of the target protein and, conversely, removing destabilization domains can increase stability/concentration of the target protein, but the instant method only indicates steps which would result in increasing the concentration of the target protein. Furthermore, there are no steps provided which would result in addition of destabilization domains to the target protein in the cell. Therefore, the rejection of claims for not being enabled for a method for regulating the concentration of a target protein in a cell as indicted herein is appropriate.

It is pointed out that amending the claim to a method of increasing the concentration of a target protein in a cell (as indicated above) would obviate the rejection. Alternatively, adding steps to the method which would result in the addition of destabilization domains may also overcome this rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
Art Unit 1635